Stem Cell Research 47 (2020) 101887

Contents lists available at ScienceDirect

Stem Cell Research

journal homepage: www.elsevier.com/locate/scr

Access to stem cell data and registration of pluripotent cell lines: The Human Pluripotent Stem Cell Registry (hPSCreg)

Nancy Mah[a,*], Stefanie Seltmann[a], Begoña Aran[b], Rachel Steeg[c], Johannes Dewender[a], Nils Bultjer[a], Anna Veiga[b], Glyn N. Stacey[d,e,f], Andreas Kurtz[a]

[a] Berlin-Brandenburger Centrum für Regenerative Therapien (BCRT), Charité – Universitätsmedizin Berlin, Berlin, Germany
[b] Stem Cell Bank, Regenerative Medicine Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain
[c] Fraunhofer UK Research Ltd, Technology and Innovation Centre, Glasgow, UK
[d] ISCBI, Barley, UKSSCBio Ltd, Barley, UK
[e] National Stem Cell Resource Centre, Institute of Zoology, Chinese Academy of Sciences, Beijing 100190, China
[f] Innovation Academy for Stem Cell and Regeneration, Chinese Academy of Sciences, Beijing 100101, China

A B S T R A C T

The value of human pluripotent stem cells (hPSC) in regenerative medicine has yet to reach its full potential. The road from basic research tool to clinically validated PSC-derived cell therapy products is a long and winding one, leading researchers, clinicians, industry and regulators alike into undiscovered territory. All stakeholders must work together to ensure the development of safe and effective cell therapies. Similarly, utilization of hPSC in meaningful and controlled disease modeling and drug screening applications requires information on the quality and suitability of the applied cell lines. Central to these common goals is the complete documentation of hPSC data, including the ethical provenance of the source material, the hPSC line derivation, culture conditions and genetic constitution of the lines. Data surrounding hPSC is scattered amongst diverse sources, including publications, supplemental data, researcher lab books, accredited lab reports, certificates of analyses and public data repositories. Not all of these data sources are publicly accessible nor associated with metadata nor stored in a standard manner, such that data can be easily found and retrieved. The Human Pluripotent Stem Cell Registry (hPSCreg; https://hpscreg.eu/) was started in 2007 to impart provenance and transparency towards hPSC research by registering and collecting standard properties of hPSC lines. In this chapter, we present a short primer on the history of stem cell-based products, summarize the ethical and regulatory issues introduced in the course of working with hPSC-derived products and their associated data, and finally present the Human Pluripotent Stem Cell Registry as a valuable resource for all stakeholders in therapies and disease modeling based on hPSC-derived cells.

1. Introduction

1.1. Stem cells in regenerative medicine

Stem cell therapy has garnered unprecedented fame and infamy in the last two decades, skyrocketing in part to the breakthrough discovery of induced pluripotent stem cells (iPSC) in 2006 (Takahashi and Yamanaka, 2006). Prior to iPSC, the field of stem cell research was driven by embryonic stem cells (ESC) and somatic stem cells (SSC), each with its own advantages and disadvantages. While human ESC have the versatility to form hundreds of cell types from all three germ layers, their routine use as an unlimited source of pluripotent cells is confronted with ethical considerations and restrictive regulations regarding the use of donated human embryos leftover from IVF treatment (Reisman and Adams, 2014). The sources of somatic stem cells, on the other hand, do not rely on ethically sensitive embryonic material and are easier to access. Importantly for cell-based therapies, patient-derived SSC represent a renewable source of autologous cells, which should in principle reduce the risk of transplant rejection. However, SSC are multipotent or unipotent and are only able to differentiate into cell types of the same lineage, and may have limited proliferation ability, thus hampering large-scale production (Reisman and Adams, 2014). Currently, SSC have therapeutic applications using hematopoeitic (blood disorders), mesenchymal (blood disorders, graft-vs-host disease, cartilage repair), epithelial (burn wounds), and limbal stem cells (ocular burns) (Ahrlund-Richter et al., 2009). SSC for clinical use form the basis for more than 500 clinical studies in the US alone (ClinicalTrials.gov, 2018). However, there only 11 SSC-based therapies with marketing authorization in the EU or United States and 20 worldwide (Abou-El-Enein et al., 2016; Cuende et al., 2018).

No longer limited to stem cells of restricted lineage, such as bone marrow stromal cells or adipose-derived stromal cells, researchers can now add to their toolbox the progenitor of almost all cells, the induced pluripotent stem cell. Human iPSCs (hiPSC) can be generated from a variety of cell types spanning a spectrum of plasticities, from germ and neural stem cells to differentiated somatic cells such as fibroblasts and

* Corresponding author.
E-mail address: nancy.mah@ibmt.fraunhofer.de (N. Mah).

https://doi.org/10.1016/j.scr.2020.101887
Received 27 May 2019; Accepted 19 June 2020
Available online 27 June 2020

peripheral blood mononuclear cells. In contrast to hESC, the generation of hiPSC does not require working with embryonic material and therefore the complicated legal and ethical issues associated with embryo destruction do not apply (Carvalho and Ramalho-Santos, 2013 Jun; Zheng, 2016). Generating iPSC requires more hands-on cell manipulation than ESC or SSC, which are typically isolated from existing tissue structures and are usually not reprogrammed before use in cell therapy. There are a variety of protocols available to generate hiPSC, using genome-integrating methods, such as retroviruses and lentiviruses, and non-genome integrating methods, such as reprogramming mediated by Sendai virus, episomal vectors, mRNA/miRNA and small molecules (Augustyniak et al., 2014; Wu et al., 2013), but in the end, the hiPSC should recapitulate the main properties of hESC, namely: 1) ability to self-renew; and 2) the ability to form cells from each of the three germ layers. For research lines with potential clinical applications, the quality of the hiPSC cells is of utmost importance. Reprogramming to hiPSC can introduce genetic aberrations, which could have detrimental downstream effects for disease modeling and clinical safety. For example, long-term passaging of PSC can lead to the selection of cells with chromosomal duplications that support a growth advantage (Merkle et al., 2017; Ben-David et al., 2014). These genetic aberrations may preclude usage of such lines for clinical application, as there is a risk that these lines could form tumors in the patients.

The versatility of deriving specific cell types from hPSC is especially promising for the treatment of diseases in which the desired therapeutic cell types are not accessible in practice. These cell types include retinal pigmented epithelia (for retinal diseases) and myoblasts (for myopathy) (Mitjavila-Garcia et al., 2005). In principle, a patient's own iPSC can be generated as a source of autologous cells; however, in practice, developing a patient-specific line for individual cell therapy is too expensive and may take too long as an ad hoc approach for an effective therapeutic intervention. Rather, it has been proposed that HLA homozygous hiPSC banks could be established to provide allogenic immunocompatible cells on-demand (Wilmut et al., 2015) (see also Lanza et al., 2019). There are also more radical approaches to providing "one-size-fits-all" immunocompatible hPSC lines, such as the creation of hPSC lines that lack MHC class I and II molecules using genome editing methodologies (Mitjavila-Garcia et al., 2005).

1.2. Uncomfortable bedfellows: shady stem cell clinics

Though stem cell therapies have been successfully applied in the form of hematopoietic stem cell transplantation for over 30 years (Thomas, 1999), and current availability of hPSCs affords the possibilities of off-the-shelf products for cell-specific therapy, disease modeling, and drug testing, stem cell therapy is in danger of becoming a victim of its own success. The hype surrounding stem cell research has attracted false claims in the form of stem cell clinics that market unproven treatments to susceptible patients. In an act of "scienceploitation" (Murdoch et al., 2018), these clinics use the publicity from basic science, such as the discovery of hiPSC cells, and feed off the success of other stem cell treatments, such as bone marrow transplants to treat acute myeloid lymphoma (AML), to sell their dubious stem cell treatments. Many of these stem cell clinics operate as direct-to-consumer businesses and charge hefty fees (Glassberg et al., 2018; Knoepfler and Turner, 2018), spawning a whole new stem cell tourism industry (Glassberg et al., 2018; Knoepfler and Turner, 2018; Rubin, 2018). Furthermore, unscrupulous stem cell clinics often use "tokens of scientific legitimacy", such as testimonials, registration of patient-sponsored clinical trials on ClinicalTrials.gov, and certifications or accreditations to appear as regulated, legitimate stem cell clinics (Gunter et al., 2010; Sipp et al., 2017; Sugarman et al., 2018). Mass media stories of celebrities who partake in stem cell tourism appear to endorse these unregulated treatments, with little critical discussion of the actual efficacy and safety of the treatment (Du et al., 2016; Rachul and Caulfield, 2015). Unregulated stem cell treatments have caused adverse events such as blindness, tumor formation, brain hemorrhaging and even death (Bauer et al., 2018).

In response to the growing number of predatory stem cell clinics and adverse events being reported in the scientific literature and the mass media, regulatory authorities have attempted to tighten up regulations. In the EU, the European Union Tissue and Cells Directives (EUTCD) was initiated in 2004 (The European Parliament and the Council of the European Union, 2019) to regulate the use of tissues and cells intended for human application and covers the early stages of hPSC derivation (see Abranches et al., 2020). Subsequently, all cell therapy products became subject to regulation as Advanced Therapy Medicinal Products (ATMP) in 2007, with a compliance transition period from 2008 to 2011 (The European Parliament and the Council of the European Union, 2018). In 2017, the FDA closed some regulatory loopholes surrounding the use of human cell- and tissue-based products (HCT/P) (Charo and Sipp, 2018). These most recent regulations are unavoidably applicable to the up-and-coming hPSC-derived cell-based therapies.

1.3. Stakeholder engagement

To ensure a smooth transition of PSC-derived cell-based therapies to market, all stakeholders, including basic and clinical researchers, stem cell banks, industry, regulatory authorities and finally the end-users (namely patients who would benefit from the therapy), must diligently participate in the development of cell-based therapies. Proponents of PSC-derived cell treatments must actively develop quality standards for

Table 1
Professional societies, institutions or resources for stem cell research and applications.

Organization	Description	Resources
International Society for Stem Cell Research (ISSCR)	global professional society of stem cell scientists and clinicians	information brochures for prospective patients of stem cell treatments (International Society for Stem Cell Research (ISSCR)); guidelines for clinicians regarding stem cell treatments (International Society for Stem Cell Research (ISSCR))
Eurostemcell	EC-funded science communication project for stem cells and regenerative medicine	diverse on-line resources for the general public and educational material (EuroStemCell)
California Institute for Regenerative Medicine (CIRM)	an institute created by the State of California to fund stem cell research for therapies	information for the general public about stem cell biology and stem cell treatments (California Institute for Regenerative Medicine (CIRM))
International Society for Cell & Gene Therapy (ISCT)	global professional society of researchers, clinicians, regulators, technologists and industry partners	annual reports on cell and gene therapy market authorizations, collection of news announcements on stem cell treatments (ISCT)
Global Alliance for iPSC Therapy (GAiT)	international consortium of public and private partners to support the development of hiPSC therapies	quality control guidelines for clinical-grade hiPSC lines (Global Alliance for iPSC Therapies (GAiT), ISCI; Sullivan et al., 2018)
International Stem Cell Initiative (ISCI)	worldwide collaborative effort of basic scientists to establish standards for PSC-based applications in human medicine	systematic performance testing to address the robustness of stem cell protocols across diverse laboratories, with the aim of establishing consensus protocols (ISCI)
International Stem Cell Banking Initiative (ISCBI)	global network of stem cell banks	publication of guidance documents regarding the international standards for banking, characterisation and testing (ISCBI)

stem cell products in consultation with regulators. Representatives from academia and industry have organized themselves into professional societies such as the ISSCR, ISCT, ISCI, GAiT and ISCBI (Table 1), with the aim of safeguarding the development of safe and effective PSC-derived cell products by working towards an international consensus on the best practices and standards for cell therapies (Andrews et al., 2015). The public must have easy access to trustworthy information about stem cell treatments. Public engagement by academic organizations is key to educating and providing reliable information on stem cell research and stem cell treatments to the public at large (Table 1). By arming patients with knowledge, patients can empower themselves and make better decisions in consultation with their physicians.

Concurrent to these developments, advances in the diversity and availability of hPSC lines should contribute to a large resource of reagents and knowledge on the particular properties and characteristics of hPSC lines. Joint initiatives with the European Commission (EC) and industry have spawned projects to generate and bank hiPSC in a quality-controlled manner (see also other chapters Sullivan, in press). Of great interest for disease modeling and drug testing are hiPSC lines derived from donors with a diagnosed disease and their gene-corrected hiPSC lines as isogenic controls, or alternatively, lines from normal donors and their genetically modified lines containing one or more disease-associated mutations. In the joint banking initiative European Bank for induced Pluripotent Stem Cells (EBiSC) (De Sousa et al., 2017), over 1100 hiPSC lines have been earmarked for banking, which include those banked directly by the EBiSC consortium (as commissioned or existing hiPSC lines) and hiPSC lines obtained through collaborations with other projects (BADiPS, HipSci, StemBANCC, and UnTangle2). Approximately 70% of these lines (Fig. 1) are actively stocked and distributed by the European Collection of Authenticated Cell Cultures (ECACC (Public Health England, 2019)). The parental hiPSC lines are largely derived from normal donors and donors with neurological diseases, followed by hiPSC lines derived from other disease groups, including blood, cardiovascular, eye, multi-systemic syndromes and muscular diseases (Fig. 2). Six parental hiPSCs have been genetically modified, such as introduction of a genetic modification associated with disease, giving rise to a total 42 pairs of isogenically modified subclone lines (Table 2). All of these parental and subclone hiPSC lines are registered in hPSCreg and are banked, making these lines an excellent resource for disease modeling studies.

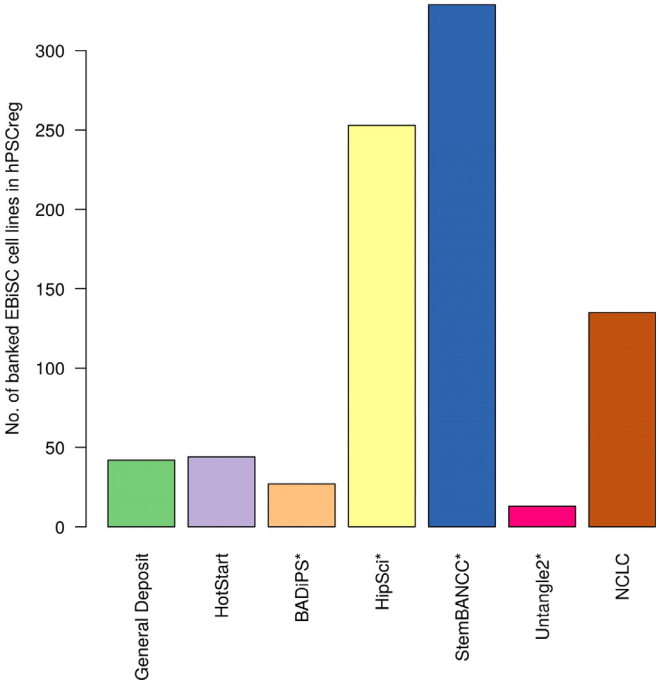

Fig. 1. Banked EBiSC Lines in hPSCreg. The EBiSC consortium banked 843 hiPSC lines, which can be categorized by origin: General Deposit = a regular cell line deposit, which was not associated to a specific project within EBiSC; HotStart = a set of hiPSC lines initially banked by EBiSC to establish the operational banking workflow (De Sousa et al., 2017); BADiPS = a CRACK IT innovation platform project for bipolar affective disorder (CRACK IT, 2019); HipSci = a large collection of well-characterised hiPSC lines for research (Streeter et al., 2017); StemBANCC = a large collection of well-characterised lines for disease modeling and toxicology studies (Morrison et al., 2015); UnTangle2 = a CRACK IT innovation platform project for Alzheimer's disease (CRACK IT, 2019); NCLC = new cell lines commissioned by the EBiSC consortium; * = hiPSC lines were banked by EBiSC as part of an hiPSC project collaboration.

1.4. Science-based medicine: quality PSC-derived cells for clinical trials

As of February 2019, there were 37 clinical trials involving PSC-derived cell types for macular degeneration and other eye disorders, which are the most treated indication in current clinical trials with hPSC derivatives (Schwartz et al., 2015; Song et al., 2015; Mandai et al., 2017; Mehat et al., 2018), but trials for other conditions such as spinal cord injury, diabetes, heart disease (Menasché et al., 2018), graft-versus-host disease and Parkinson's disease are also in progress (Table 3) (Guhr et al., 2018). Thirty-one trials used hESC-derived cells, and the remaining six involved hiPSC derivatives (including one autologous application). Most trials are being carried out in the USA (12 trials), with China and the UK with 7 and 5 clinical trials, respectively. Japan is leading in performing clinical trials involving hiPSC-derivatives. Five of the six trials using hiPSC-derivatives are located in this country. All of these hPSC-derived cell products are still in the stages of drug development (Phase I/II/III). Currently, not a single hPSC-derived cell product has reached the marketing authorization stage.

Some organizations have announced upcoming clinical trials with hiPSC-derived cardiac cells for ischemic heart disease (Osaka University) and with hiPSC-derived killer T cells (Thyas Co. Ltd.) and natural killer cells for immunotherapy for some kinds of cancer and for hematologic malignancies (Fate Therapeutics, Inc.) (The Asahi Shimbun, 2018; Globe Newswire, 2019; Fate Therapeutics, 2019). It should be noted that collecting information from the clinical trials in progress or about to start is difficult as data are not available in the literature. When available, press releases or other non-scientific sources have been used and as a consequence, the scenario described is probably very incomplete. Establishing an efficient registry for clinical trials with hPSC derivatives is therefore a foremost need.

Human PSC-derived cell therapies present new regulatory challenges. hPSC-derived cells are produced in multiple steps of cell engineering and sometimes genetic engineering, which may span a total time culminating in weeks or months from cell reprogramming to directed differentiation, in order to manufacture the final product with the desired properties. At any point in the long chain of hPSC-derived cell product development, unexpected genomic alterations may accumulate in the cells, leading to an uncertain risk for the recipient of the cell therapy. Considering that the cells may persist for the rest of recipient's life, consideration must be given to the purity and stability of the hPSC-derived cells such that the cell product is neither contaminated with nor differentiates to unwanted cell types (Petricciani et al., 2017). Therefore, the quality of both the hPSC cells and the specific cell types that have been derived from the hPSC cells must be proven before the hPSC-derived cells can be safely used in clinical trials. It is therefore of utmost importance that certain standard criteria must be fulfilled to ensure high quality hPSC cells, and that this data is transparent and comparable to hPSC lines generated worldwide. A similar high standard of cell quality is necessary for their use in disease modeling and drug screening, as genetic alterations, for example, can severely bias the models and test data.

To strengthen public and scientific assurance in hPSC-based

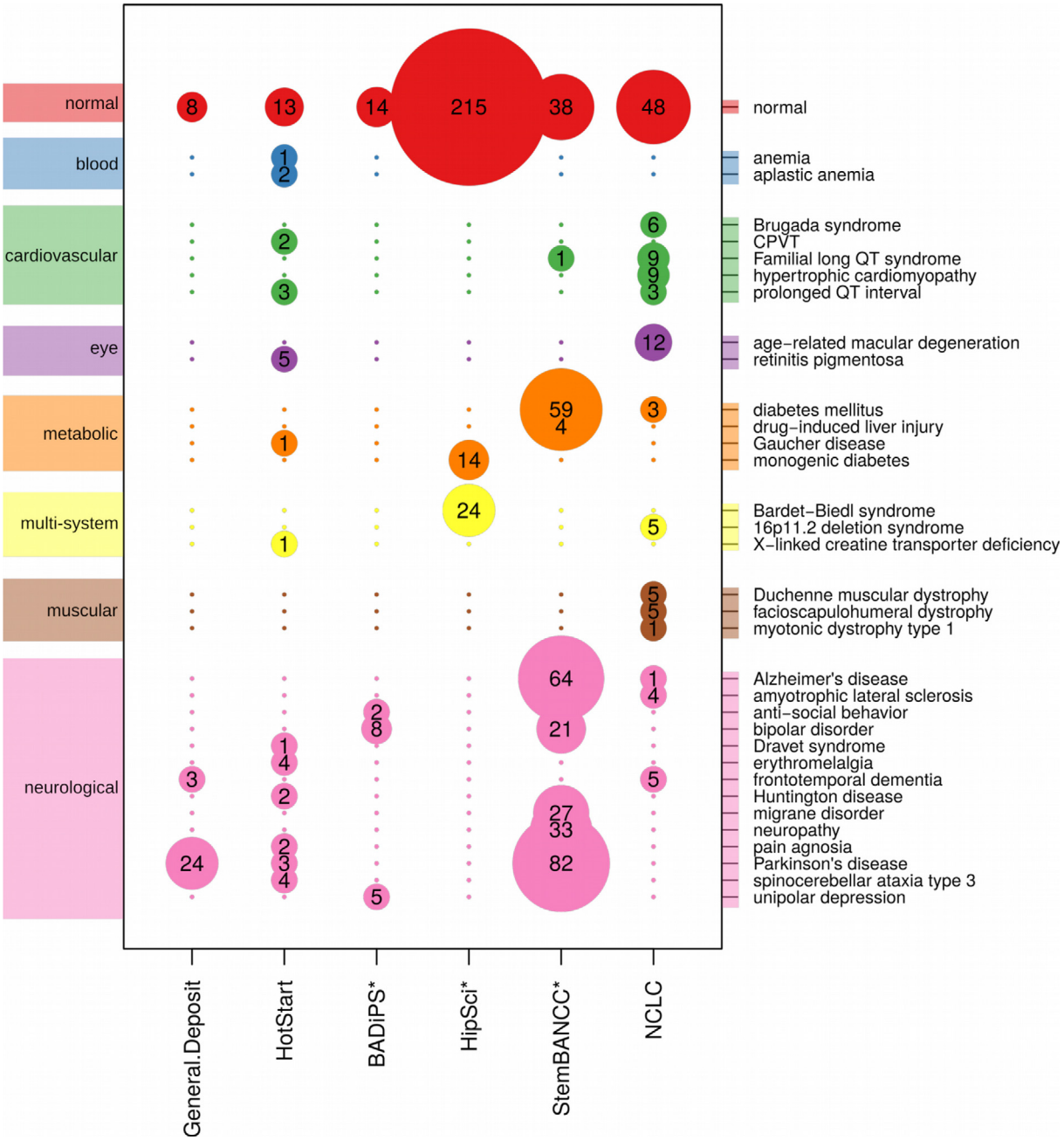

Fig. 2. Overview of EBiSC banked parental hiPSC lines registered in hPSCreg and associated diseases with these lines. Parental hiPSC lines were generated from donors with and without disease. Each column represents the projects and each row represents the disease status, which is grouped into eight broad categories: normal (red), blood (blue), cardiovascular (green), eye (purple), metabolic (orange), multi-system syndrome (yellow), muscular (brown), and neurological (pink). The diameter of the coloured circles is approximately proportional to the actual number of lines, which is printed in the middle of each circle. Abbreviations: CPVT = catecholaminergic polymorphic ventricular tachycardia; 16p11.2 deletion syndrome = Chromosome 16p11.2 deletion syndrome, 220kb (distal 16p11.2 microdeletion syndrome). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

therapies, steps must be taken to ensure foremost patient safety. The first ever clinical trial involving hiPSC-derived cells was led by Masayo Takahashi in Japan. In this trial, the transplantation of hiPSC-derived retinal pigmented epithelial cells in a second patient (male) was halted, partly because the cells were found to contain deletions on the X chromosome (Mandai et al., 2017). Though the authors of the study admitted that the cancellation of the second transplantation was perhaps "unnecessarily strict" (Mandai et al., 2017), the first patient had no serious complications one year after therapy, and this clinical trial in itself was a milestone for regenerative medicine (Reardon and Cyranoski, 2014). Taking advantage of a change in the Japanese law, by which the Japanese government decided to only allow the use of allogeneic, matched hiPSC from cryobanks, the Takahashi team put in place a new clinical trial for the same indication using allogenic hiPSC.

1.5. Securing the pathway to successful clinical translation

The smooth implementation of hPSC-based cell therapies will require a concerted effort from all stakeholders with a vested interest in safe and effective clinical translation of hPSC-based cell therapies. Human PSC lines with the "right stuff", in terms of ethical provenance, biological quality and safety, cell line authenticity and immunological properties, are in demand. Background information regarding the generation of these cell lines must be available, including traceable

Table 2
Genetically modified hiPSC lines banked by the EBiSC project.

Parental line standard name	Donor disease status	Standard name of modified line	Disease associated with genetic modification	Modified Locus
BIONi010-C	normal	BIONi010-C-10	monogenic diabetes	HNF1A
		BIONi010-C-11	monogenic diabetes	HNF1A
		BIONi010-C-12	monogenic diabetes	HNF4A
		BIONi010-C-13	modification not disease-related	AAVS1
		BIONi010-C-15	modification not disease-related	AAVS1
		BIONi010-C-17	Alzheimer's disease	TREM2
		BIONi010-C-18	inflammatory diseases and cancer	TBK1
		BIONi010-C-2	Alzheimer's disease	APOE
		BIONi010-C-3	Alzheimer's disease	APOE
		BIONi010-C-4	Alzheimer's disease	APOE
		BIONi010-C-5	Alzheimer's disease	CD33
		BIONi010-C-6	Alzheimer's disease	APOE
		BIONi010-C-7	Alzheimer's disease	TREM2
		BIONi010-C-8	Alzheimer's disease	TREM2
		BIONi010-C-9	Alzheimer's disease	CD33
BIONi037-A	normal	BIONi037-A-1	Alzheimer's disease	APOE
		BIONi037-A-2	Alzheimer's disease	APOE
		BIONi037-A-3	Alzheimer's disease	APOE
		BIONi037-A-4	Alzheimer's disease	APOE
EDi001-A	Parkinson's disease	EDi001-A-1	Parkinson's disease	SCNA
		EDi001-A-2	Parkinson's disease	SCNA
		EDi001-A-3	Parkinson's disease	SCNA
		EDi001-A-4	Parkinson's disease	SCNA
SIGi001-A	normal	SIGi001-A-1	modification not disease-related	SLC17A7
		SIGi001-A-10	*multiple neurodegenerative diseases	MAPT
		SIGi001-A-11	*multiple neurodegenerative diseases	MAPT
		SIGi001-A-12	frontotemporal dementia	MAPT
		SIGi001-A-13	Alzheimer's disease	MAPT
		SIGi001-A-2	modification not disease-related	SLC17A7
		SIGi001-A-3	frontotemporal dementia	MAPT
		SIGi001-A-4	frontotemporal dementia	MAPT
		SIGi001-A-5	frontotemporal dementia	MAPT
		SIGi001-A-6	frontotemporal dementia	MAPT
		SIGi001-A-7	frontotemporal dementia	MAPT
		SIGi001-A-8	*multiple neurodegenerative diseases	MAPT
		SIGi001-A-9	*multiple neurodegenerative diseases	MAPT
STBCi006-A	Alzheimer's disease	STBCi006-A-1	Alzheimer's disease	APOE
		STBCi006-A-3	Alzheimer's disease	APOE
		STBCi006-A-4	Alzheimer's disease	APOE
UKBi011-A	Alzheimer's disease	UKBi011-A-1	Alzheimer's disease	APOE
		UKBi011-A-3	Alzheimer's disease	APOE
		UKBi011-A-4	Alzheimer's disease	APOE

* Associated with three neurodegenerative diseases: corticobasal degeneration/FTDP-17 (Frontotemporal dementia and parkinsonism linked to chromosome 17)/ progressive supranuclear palsy.

protocols for derivation and maintenance, and thoroughly documented genetic modifications, if performed. Moreover, banked hPSC lines are added-value reagents that have the potential to augment basic and clinical research by encouraging the re-use of existing lines, thereby conserving resources. Having this body of information is imperative to enable the evaluation of hPSC lines for their potential and suitability in specific clinical applications. A central resource that contains hPSC line information in a standardized manner would greatly enhance clinical translation of hPSC lines by facilitating the search for suitable hPSC lines and simplifying the information gathering process for the compilation of a potential clinical product dossier. The Human Pluripotent Stem Cell Registry (hPSCreg) provides a framework to collect and store hPSC line data to fulfill these needs.

2. The Human Pluripotent Stem Cell Registry

2.1. Enabling qualified pluripotent stem cell lines

The Human Pluripotent Stem Cell Registry was launched in 2007 to facilitate an overview of pluripotent stem cell lines used in research funded by the European Commission (EC) (Seltmann et al., 2016). Since its inception over a decade ago, hPSCreg has grown to contain 739 human ESC and 1868 human iPSC lines from 30 countries worldwide (as of February 2019). The Registry addresses several important aspects surrounding hPSC lines:

Donor consent: the conditions under which consent were obtained and what was consented to are fundamental to the ethical and lawful usage of the biological materials.

Applicable local laws: the geographical location where the tissue donations were made and the hPSC cells were derived, as well as the date of derivation (especially in the case of hESC), may influence hPSC line usage according to local laws.

Biological origin and derivation: clinical and phenotypic data from the donor of the source material, the materials and methods used to derive the hPSC, as well as any genetic modifications that may have been introduced, have a bearing on the line's suitability for downstream applications, such as drug-testing, disease modeling or cell therapy. The starting biological material and subsequent experimental procedures must be traceable.

Evidence of pluripotency: as there are a diverse number of tests available to show self-renewal and pluripotency, the hPSC line must satisfy a minimum set of criteria to demonstrate these characteristics.

Authenticity: the identity of the line in further research should be unambiguous through the use of short tandem repeat (STR) typing and standard cell nomenclature.

Standard data collection: the data surrounding the hPSC lines should

Table 3
Update of clinical trials involving hPSC-based cell therapies.

Sponsor	Diseases	Study ID	Cell Origin	Phase	Country
Assistance Publ. - Hôp. Paris	Ischemic Heart Disease	NCT02057900	hESC	I	France
Astellas Inst. Regen.Med.	Stargardt's Macular Dystrophy	NCT01469832	hESC	I/II	UK
Astellas Inst. Regen.Med.	Stargardt's Macular Dystrophy	NCT01345006	hESC	I/II	USA
Astellas Inst. Regen.Med.	Dry Age-Related Macular Degeneration	NCT01344993	hESC	I/II	USA
Astellas Inst. Regen.Med.	Age-Related Macular Degeneration	NCT02463344	hESC	I/II	USA
Astellas Inst. Regen.Med.	Stargardt's Macular Dystrophy	NCT02445612	hESC	I/II	USA
Astellas Inst. Regen.Med.	Stargardt's Macular Dystrophy	NCT02941991	hESC	I/II	UK
Astellas Inst. Regen.Med.	Age-Related Macular Degeneration	NCT03178149	hESC	I/II	USA
Astellas Inst. Regen.Med.	Macular Degenerative Disease	NCT03167203	hESC	I/II	UK/USA
Asterias Biotherapeutics, Inc.	Spinal Cord Injury	NCT01217008	hESC	I	USA
Asterias Biotherapeutics, Inc.	Spinal Cord Injury	NCT02302157	hESC	I/II	USA
Cell Cure Neurosciences Ltd	Age-Related Macular Degeneration	NCT02286089	hESC	I/II	Israel
CHABiotech CO., Ltd	Dry Age Related Macular Degeneration	NCT01674829	hESC	I/IIa	Korea
CHABiotech CO., Ltd	Stargardt's Macular Dystrophy	NCT01625559	hESC	I	Korea
Chinese Academic of Science	Dry Age-Related Macular Degeneration	NCT03046407	hESC	I/II	China
Chinese Academy of Sciences	Dry Age-Related Macular Degeneration	NCT02755428	hESC	I	China
Chinese Academy of Sciences	Dry Age-Related Macular Degeneration	ChiCTR-OCB-15007054	hESC	I	China
Chinese Academy of Sciences	Retinitis Pigmentosa Diseases	ChiCTR-OCB-15007055	hESC	I	China
Chinese Academy of Sciences	Parkinson's Disease	NCT03119636	hESC	I/II	China
Cynata Therapeutics	Graft versus Host Disease	NCT02923375	hiPSC allog.	I	Australia
Cyto Therapeutics Pty Limited	Parkinson's Disesase	NCT02452723	phESC	I	Australia
Eye Institute Xiamen University	Severe Ocular Surface Disease	ChiCTR-OCB-15005968	hESC	I/II	China
Federal University of São Paulo	ARMD, Starg.D, EARMD	NCT02903576	hESC	I/II	Brazil
Keio University	Spinal Cord Injury	see reference (Japan approves world-first trial using iPS cells to treat spinal cord injuries, 2019)	hiPSC	–	Japan
Kobe City Med. Center Hosp.	Wet Age-Related Macular Degeneration	UMIN000026003	hiPSC allog.	I	Japan
Kyoto University Hospital	Parkinson's Disease	UMIN000033564	hiPSC allog.	I/II	Japan
Kyoto University Hospital	Parkinson's Disease	UMIN000033565	hiPSC allog.	III	Japan
Pfizer	Wet Age-Related Macular Degeneration	NCT01691261	hESC	I	UK
Pfizer	Wet Age-Related Macular Degeneration	NCT03102138	hESC	I	UK
Regenerative Patch Tech, LLC	Dry Age-Related Macular Degeneration	NCT02590692	hESC	I/II	USA
RIKEN Center for Dev. Biol	Wet Age-Related Macular Degeneration	UMIN000011929	hiPSC autol.	I	Japan
Southwest Hospital, China	Macular Degeneration Diseases	NCT02749734	hESC	I/II	China
ViaCyte	T1 Diabetes Mellitus	NCT02239354	hESC	I/II	USA
ViaCyte	T1 Diabetes Mellitus	NCT03162926	hESC	I	USA
ViaCyte	T1 Diabetes Mellitus	NCT03163511	hESC	I/II	USA
ViaCyte	T1 Diabetes Mellitus	NCT02939118	hESC	I/II	USA
ViaCyte	T1 Diabetes Mellitus	see reference (ViaCyte, 2019)	hESC	I/II	Belgium

Abbreviations: ARMD: age-related macular degeneration; Starg.D.: Stargardt's disease; EARMD: exudative age-related macular degeneration; allog.: allograft; autol.: autologous; phESC = parthenogenetic stem cell line.

follow the FAIR data principles, such that the data is findable, accessible, interoperable and re-usable according to the guidelines proposed by the Future of Research Communications and e-Scholarship (FORCE11) (FORCE11, 2018).

All of these aspects lend transparency to the process of making and using these lines for research and clinical applications. HPSC lines that meet a minimum criteria for ethical provenance and pluripotency are eligible to receive certificates, which are recognized by EC funding bodies as evidence for qualified hPSC lines for use in EC-funded research. For researchers, the registration of their hPSC lines in hPSCreg gives them more visibility and recognition for their work, as the lines receive unique names and this traceable information is shared between many databases, such as Cellosaurus (hosted by the Swiss Institute of Bioinformatics (Bairoch, 2018) and BioSamples (hosted by European Molecular Biology Laboratory - European Bioinformatics Institute (European Molecular Biology Laboratory, xxxx). Furthermore, researchers have the option of publishing their lines as a lab resource in the journal Stem Cell Research. For funders and industry, hPSCreg gives an overview of which lines are in use and who is producing hPSC lines, such that future funding calls can be designed to encourage future development of hPSC lines and their derivatives, for example, into disease areas of major public health concern. Also, there are opportunities to quantify the amount of publicly funded hPSC-related research and the success of its outcomes in terms of clinical translation and technology transfer. For regulators, hPSCreg provides a convenient oversight of the generation and production of starting materials for future hPSC-derived cell therapy products, such that regulators have relevant information to prepare for clinical trials involving novel hPSC-derived cell therapy products. Stakeholders from the entire range of the clinical development process can benefit from the registration of hPSC lines in hPSCreg.

2.2. Registering lines in hPSCreg

To facilitate data collection, hPSCreg has implemented a self-regulating user management process. To register a hPSC line, the organization that generated the line must be registered in hPSCreg. Current details of the user registration process can be found in the “Quick-Start Guide” on the hPSCreg website (The Human Pluripotent Stem Cell Registry (hPSCreg), 2018). Briefly, the user management system is self-regulating in that it allows previously registered hPSCreg users to approve user registrations originating from the same institution, in a peer-to-peer trust mode. The user management system also provides a way to automatically use the generating organization's acronym in composing the standard nomenclature of the hPSC lines.

The first step in registering a line is to acquire an automatically generated standard name by choosing the hPSC line type (currently embryonic stem cell or induced pluripotent stem cell line), the generator institution, and relations to other hPSC lines in hPSCreg (i.e. whether it is another hPSC line from a previously registered donor or it is a subclone of another previously registered hPSC line). Second, all data associated with the hPSC line can be entered. The on-line registration of hPSC lines is divided into eight headings as outlined in Table 4, and a brief overview of the registration process is depicted in Fig. 3. The user-entered data can be saved at any point in the data entry process, so that it is possible to resume data entry at a later time. Alternatively, if a user wishes to register multiple cell lines at a time, a block registration of lines could be carried out by contacting hPSCreg directly for a mass data import (see also the “Access to Data” section below). Each section in the data entry process has some required fields, which must be provided before the user can submit the line for validation by the hPSCreg validator. These mandatory fields include key information, such as the conditions of donor consent and the cell line's permitted uses and availability, characterization of pluripotency, and genetic information. A detailed description of the mandatory fields can be viewed in the “Cell Line Registration Quick-Start Guide” from the hPSCreg website (The Human Pluripotent Stem Cell Registry (hPSCreg), 2018). Once the mandatory information fields have been filled, the registrant can submit the line for validation. The hPSCreg validator will evaluate the data provided about the hPSC line and validate the line according to the criteria for validation in the “Documents and Governance” section of the hPSCreg website (The Human Pluripotent Stem Cell Registry (hPSCreg), 2019). Data from lines that have been registered in hPSCreg, but are missing mandatory information and have not yet been submitted for validation, will only publicize basic information about the hPSC line, such as the standard cell line name, alternative names and the generator and owner of the line. Additional information from hPSC lines, such as anonymized donor information and details about the cell line derivation, becomes publicly visible as soon as the line has been submitted for validation. Finally, submitted lines that meet ethics and pluripotency criteria are eligible to receive certificates, which can be obtained from the hPSCreg website.

2.3. Registering projects and clinical trials in hPSCreg

The results of publicly-funded research are often disseminated through publications in scientific journals or funding agency reports. To provide more transparency towards the use of hPSC lines, users can register research projects in hPSCreg by entering basic information about a project (i.e. title, short name, description, funder, institution) and then associating already registered hPSC lines with the project information. This information will support communication between laboratories working on similar topics, or using the same hPSC lines, and thus help to reduce redundancies and build synergies. In addition, project certificates together with cell line certificates provide confidence to the funders and publishers of projects that acceptable ethical and scientific standards are being observed (Fig. 4). The EC currently requests these certificates as funding requirements. Although it is not currently required by other funding agencies to register projects where hPSC lines are used, the project registration is open to all users. As of February 2019, hPSCreg had 123 registered projects, which are associated to 1789 unique hPSC lines. The most popular cell lines associated with projects were all hESC lines (WAe009-A, WAe001-A, and UOSe003-A).

A long-term goal of regenerative medicine is to be able to derive specific cell types from hPSC lines and to use these hPSC-derived cells in cell therapy or as part of medical devices. The clinical translation of hPSC-derived cells is still in its infancy, with currently (as of February 2019) no ongoing clinical trials involving hPSC-derived cells beyond Phase III anywhere in the world. hPSCreg enables registered users to record clinical trials and the associated source hPSC lines used, as well as to provide information on the specific therapeutic cell type derivation. By storing this information in a single resource, it is possible to track the success of hPSC lines in contributing to validated cell therapies. The hPSCreg clinical trial registry provides specific information, which is not readily available in other resources, and encourages exchange on quality and performance data of source cell lines and therapeutic cell products, provides insights into regulatory compliance handling and provides transparency and feedback options.

2.4. Access to data

hPSCreg strives to follow the FAIR principles (Wilkinson et al., 2016) as proposed by the FORCE11 Initiative, to make the data “Findable, Accessible, Interoperable, and Reusable”. The Registry supports the FAIRification of scientific data for hPSC research to ensure optimal reprocessing of human- and machine-readable research data.

To increase the discoverability of hPSCreg as a data resource for hPSC lines, hPSCreg is registered in the global registries of research data repositories such as re3data.org and fairsharing.org (re3data.org., xxxx, fairsharing.org., xxxx, identifiers.org., xxxx). The data within hPSCreg is findable, as each cell line in hPSCreg is assigned with a standard name that acts as a globally unique and persistent identifier.

Table 4
Organization of hPSC-associated data in hPSCreg.

Heading	Examples of Data Fields	Examples of applicable metadata items or standards
General Information	Cell line name*	Standard hPSC line name (Kurtz et al., 2018)
	Generator institution*	
	Biosamples ID of cell line*	BioSamples (Faulconbridge et al., 2014)
	Publications associated with the cell line	PubMed Identifier (NCBI)
	Is the cell line readily obtainable for third parties?*	
Donor Information	Sex*	Experimental Factor Ontology (Malone et al., 2010)
	Biosamples ID of donor*	BioSamples (Faulconbridge et al., 2014)
	Diagnosed diseases	Experimental Factor Ontology (Malone et al., 2010), Human Phenotype Ontology (Köhler et al., 2017)
Ethics/Usage	Has consent been obtained from the donor of the tissue from which iPS cells have been derived?*	Automatable Discovery and Access Matrix (ADA-M) (Global Alliance for Genomics and Health, 2018)
	Was the consent voluntarily given by the donor, custodian or parents?	
	Does consent expressly prevent derivation of iPS cells?*	
	Does consent prevent CELLS DERIVED FROM THE DONATED BIOSAMPLE from being made available to researchers anywhere in the world?*	
	Has a favourable opinion been obtained from a research ethics committee, or other ethics review panel, in relation to the PROPOSED PROJECT, involving use of donated material or derived cells?*	
Derivation	Cell type of the source cell (fibroblast, erythroblast, …)*	Experimental Factor Ontology (Malone et al., 2010), Cell Ontology (Bard et al., 2005)
	Vector type for reprogramming*	Minimum Information About a Cellular Assay for Regenerative Medicine (MIACARM) (Sakurai et al., 2016)
	Available as clinical grade	MIACARM
Culture Conditions	Surface coating	MIACARM
	Feeder cells	MIACARM
	Culture conditions: Medium*	MIACARM
Characterisation	Analysis of undifferentiated cells: marker expression*	MIACARM
	Differentiation potency (Endoderm, Mesoderm, Ectoderm)*	MIACARM
	Microbiology/virology screening	MIACARM
Genotyping	Has the cell line karyotype been analysed?*	
	Human Leukocyte Antigens (HLA) typing	HLA Nomenclature (Marsh et al., 2010)
	Short Tandem Repeat (STR) typing*	
Genetic Modification	Genetic modifications related to a disease or phenotype context*	Sequence Variant Nomenclature (den Dunnen et al., 2016)

*Data must be entered in these mandatory fields before a line can be submitted for validation by the hPSCreg validator.

Furthermore, every cell line is annotated with extensive metadata using a “plurality of accurate and relevant attributes”, as outlined by the FORCE11 initiative. Data completeness and correctness are manually checked for each line after submission based on a defined set of minimal criteria (see hPSCreg section on “Documents and Governance” (The Human Pluripotent Stem Cell Registry (hPSCreg), 2019). These criteria may be adjusted based on feedback from the hPSCreg community, for example, the hPSCreg Committee of National Representatives, a high-level advisory group of hPSC–scientists.

The standard name is linked to a unique Biosample ID for both cell line and donor. The cell lines can be searched on the webpage by name or by associated (meta)data. Given other names, synonyms, and identifiers, an API can be used to find the official hPSCreg standard unique identifier of cell lines. For example, the well-known hESC line “H9″ has the standard identifier ”WAe009-A“.

Basic information about a cell line (i.e. generating institution, hESC/hiPSC, donor number, subclone number) is publicly accessible on the website in human-readable form and by various RESTful web services (Fielding, 2000) (also known as web APIs) as soon as the cell line name has been registered by the user. Additional cell line information (i.e. ethics of tissue donation, biological properties of the cell line) will become public once the line has been submitted. Data that could be used to identify the donor like STR data is not made publicly available. Genetic data are made available for third-party use, subject to the terms of donor consent and approval by a data access committee. All data collected by hPSCreg are stored according to the General Data Protection Regulation (GDPR).

Whenever possible, ontology terms are used to annotate the cell line information. HPSCreg works with partners to find a robust solution for automated data transfer between the available data sources and targets. Data exchange with several partners is implemented mainly using the data exchange format JSON (Internet Engineering Task Force (IETF), 2017; ECMA International, 2017) which is an open standard and a human readable text format. hPSCreg has on-going collaborations for data exchange with Cellosaurus (Bairoch, 2018), Cellular Dynamics (Fujifilm, xxxx), eagle-i (Harvard Catalyst, xxxx), EBI Biosamples (Faulconbridge et al., 2014), EBiSC (De Sousa et al., 2017), GAiT (Global Alliance for iPSC Therapies (GAiT), xxxx), RIKEN (RIKEN, xxxx), Rutgers (RUCDR Infinite Biologics, xxxx) and SKIP (Stemcell Knowledge & Information Portal (SKIP), xxxx).

The existing APIs allow the reuse of the available data by other projects. Cellosaurus is already using the API as a data source for their platform, resulting in on-going data checks between Cellosaurus and hPSCreg, which increases the quality of cell data annotation and expands the visibility of hPSC lines. As of January 2019, approximately 30% of the hPSC lines collected by Cellosaurus were also registered in hPSCreg. The Integrated Collection of Stem Cell Bank data (ICSCB) (Fujibuchi Laboratory, xxxx) is using the MIACARM (Sakurai et al., 2016) API for their platform-independent cell line search.

2.5. Incentives for the registration of lines in hPSCreg

hPSCreg has to balance registrant compliance with the information burden placed on the registrant. Users are less likely to register lines if too much information is required for registration; however, there are prospective downstream benefits to line registration in hPSCreg. By registering their lines in hPSCreg, users can demonstrate their research output and quality, and increase the value and recognition for their work. Validation certificates issued by hPSCreg for qualified cell lines speaks to the ethical and scientific quality of hPSC derivation. The trend towards more transparency in terms of open science and open data will become more pronounced, as more scientific and medical journals embrace the FAIR data principles. Authors will be encouraged to thoroughly document hPSC lines generated in their manuscripts, in the

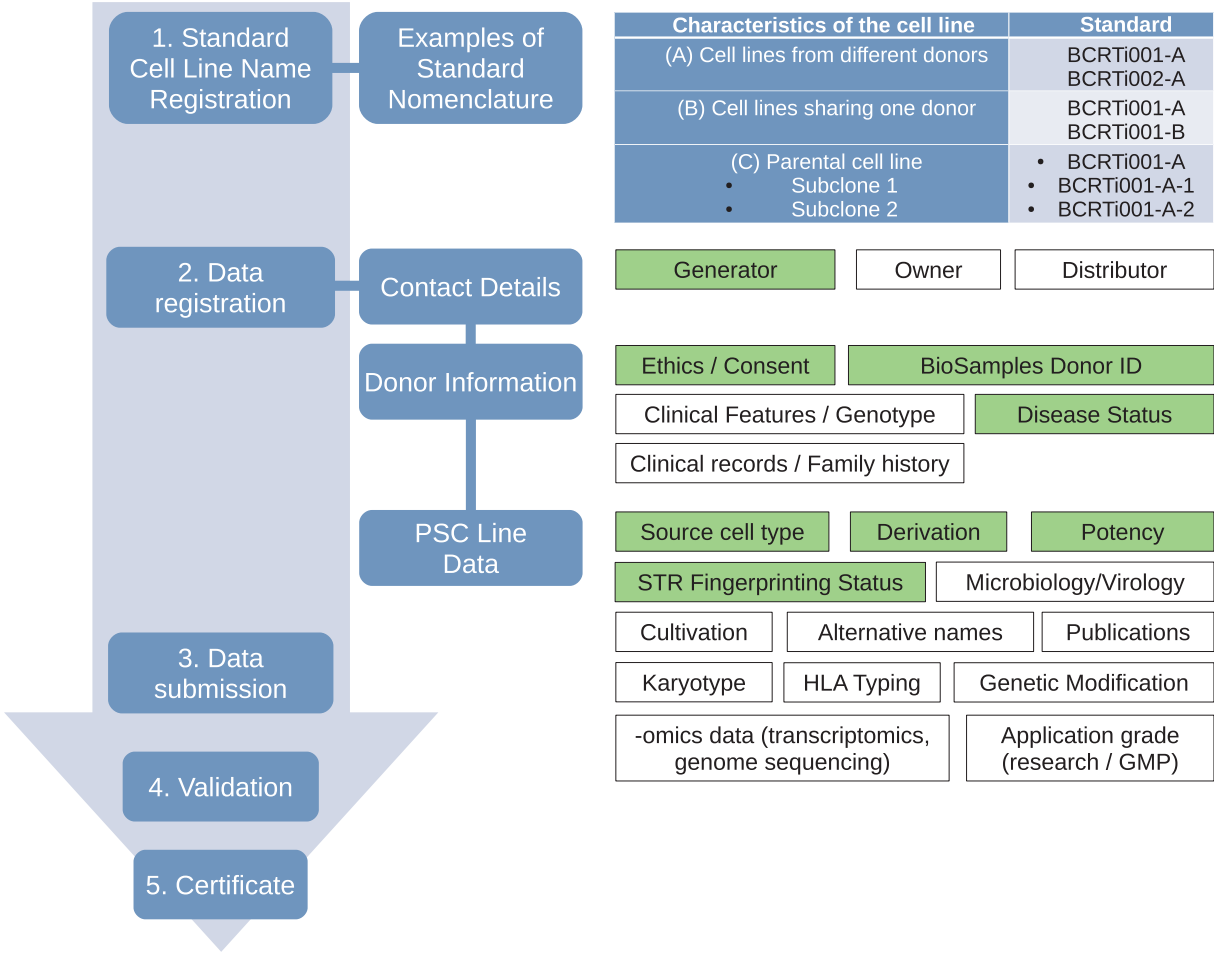

Fig. 3. Overview of Cell Line Registration in hPSCreg. First, a unique standard cell line name is assigned to the new hPSC line. The standard nomenclature contains human-readable information such as the acronym of the organization that generated the hPSC line, the hPSC type (i.e. "i" for induced pluripotent stem cell line and "e" for embryonic stem cell line), a suffix indicating the donor, such that lines from the same donor can be traced, and a second suffix indicating that a line is a subclone of an hPSC line. In the context of hPSCreg, a subclone is defined to be any PSC line which has been genetically modified, such as a modification to contain a disease mutation or reporter gene construct. Second, the user is prompted to enter contact information for the cell line, donor information and data about the hPSC line. Mandatory information is shown in green boxes. Once all mandatory information has been entered, the user can submit the line for validation (step 3). The hPSCreg validator will go through all of the mandatory information and validate the hPSC line if all data satisfies the validation criteria (step 4). Finally, lines that pass validation are eligible to receive certificates attesting the ethical and biological provenance of the hPSC line. Certificates can be obtained from the hPSCreg website. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

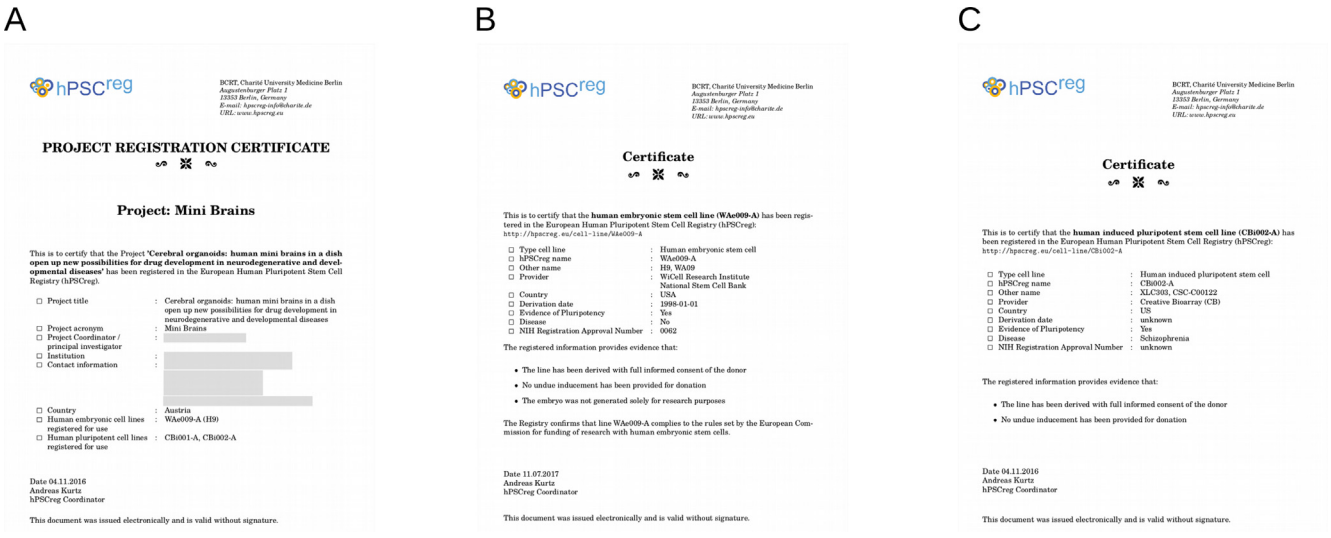

Fig. 4. Examples of certificates issued by hPSCreg. A. Project certificate. B. hESC line certificate. C. hiPSC line certificate.

same manner that transcriptome data should be deposited in a public data repository and referenced by a persistent identifier. As a central registry, hPSCreg makes this documentation possible as a FAIR resource, and reduces the burden of repeated deposition of the same information in multiple sources. As technologies progress, hPSC derivation will also become routine to the point where the derivation itself no longer merits a separate stand-alone publication. Publishing a qualified line on hPSCreg offers researchers way to have their lines disseminated and acknowledged in a manner that exceeds the superficial level of ethical evaluation carried out by journal peer review. With hPSC line data in a central registry, it will be much easier for all parties to find hPSC lines most relevant for a specific purpose and lead to more widespread use of hPSC lines. Especially, there are gains to be made through a match-making process between cell line generators and cell line seekers looking for a particular cell line for clinical translation.

3. Summary

3.1. Future outlook for hPSC data

The meticulous and judicious data collection of hPSC data must keep pace with advances and trends in technology, which will impact the clinical translation of hPSC-derived cells. To accommodate this, it is likely that hPSC line information must be collected in greater detail and new fields or concepts will have to be introduced in hPSCreg. For instance, the integration of somatic nuclear hPSC and parthenogenetic hPSC lines into hPSCreg will necessitate extensions to the standard nomenclature to properly annotate these kinds of hPSC lines. Indeed, parthenogenetic PSC lines are already being used in pre-clinical and clinical studies (Wang et al., 2018; Gonzalez et al., 2016; Hayek, 2018). Increased use of genome editing techniques, for example by CRISPR/Cas, enables researchers to routinely edit a cell line's genome to introduce mutations or to normalize existing disease mutations from patient material. Unintentional yet inevitable genetic changes may occur in hPSC line during propagation and differentiation. A risk assessment of genetic changes will be made easier by the falling costs of high-throughput DNA sequencing (Wetterstrand, 2018), which will make sequencing affordable and accessible to more researchers and enable more whole genomes and epigenomes to be analyzed at near-base resolution for any cell line. Guidelines regarding the acceptable extent of off-target gene editing or even what kinds of intentional or non-intentional modifications observed by epi-/genome sequencing constitutes an acceptable risk have not been defined and are the subject of on-going discussions in the clinical translation field (Keep off-target effects in focus, 2018; Andrews et al., 2017). In this regard, the Registry can act as an anchor to link genetic mutations and variations and registered lines such that a risk assessment meta analysis may be carried out.

3.2. Setting the stage for transparency in pluripotent stem cell research and clinical translation

The Human Pluripotent Stem Cell Registry was established with support from the EC to provide transparency in human pluripotent stem cell research. This is accomplished by: 1) collecting a standard set of data addressing ethical procurement of human material for hPSC generation, derivation and pluripotency of the hPSC lines, and usage of the lines as stipulated by the donor consent; and 2) using standard terms and ontology to annotate the hPSC-associated data, thus enabling comparability between hPSC lines generated from different institutions and countries. For instance, the adoption of specifications, such as standard cell line nomenclature and MIACARM, will improve data exchange with other stem cell databases and facilitate targeted cell line searches. Moreover, the use of Biosample Donor IDs and STR profiles should make it possible to generate trackable cell line pedigrees across all registered lines. While hPSCreg considers basic evidence of pluripotency for validation, such evidence may not reveal a line's underlying peculiarities—not all hPSC lines are equal (Lee et al., 2014; Kim et al., 2011). Some have predilections towards cell types of certain lineages due to epigenetic memory, and in fact this knowledge could be advantageous for some applications (Bar-Nur et al., 2011). Practical know-how gained while working with the lines can be valuable information to cell line seekers. To this end, hPSCreg encourages research community involvement by providing a feedback comment field for hPSC lines, where users can publicly share their cell line experiences.

The transparent process of generating hPSC lines will demonstrate the hPSC line quality and its appropriate usage for potential applications. As a biological example, older hiPSC lines may have been reprogrammed by retroviral vectors, which randomly integrate into the genome and may have unforeseen deleterious properties, such as tumorigenicity, when used as a source for hiPSC-derived lines. Such lines may be better suited for non-cell therapy applications, such as functional cells contained within a medical device. Additionally, an hPSC line may have limited applications due to its allowed usage as stated in the donor consent, for example, restriction to non-commercial use only. Therefore, transparency in hPSC data is important to avoid downstream usages incompatible with the biological and legal properties of the cell line.

Apart from cell-based therapy, hPSC lines will find increasing utility as the source material for hPSC-derived cell types for use in individualized disease modeling and drug screening. Both approaches will require the integration clinical data from the donor patient and the hPSC data, which together will be highly informative for the quality of the disease model and the accuracy of the drug screening process. These developments constitute the growth of a new data sphere, which is currently divided into several silos (Kurtz et al., 2019). HPSCreg is well-positioned to act as a key central resource for the integration of new data in a FAIR-compliant manner.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgments

We thank Mohamed Abou El-Enein, Magdi Elsallab and Amos Bairoch for their helpful comments.

Funding

This work is funded by the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement 726320 and the Innovative Medicines Initiative Grant Agreement 115582.

References

Abou-El-Enein, M., Elsanhoury, A., Reinke, P., 2016. Overcoming challenges facing advanced therapies in the EU Market. Cell Stem Cell 19 (3), 293–297.

Abranches, E., Spyrou, S., Ludwig, T., 2020. GMP Banking of Human Pluripotent Stem Cells: A US and UK perspective. Stem Cell Res. 45, 101805. https://doi.org/10.1016/j.scr.2020.101805.

Ahrlund-Richter, L., De Luca, M., Marshak, D.R., Munsie, M., Veiga, A., Rao, M., 2009. Isolation and production of cells suitable for human therapy: challenges ahead. Cell Stem Cell 4 (1), 20–26.

Andrews, P.W., Baker, D., Benvinisty, N., Miranda, B., Bruce, K., Brüstle, O., et al., 2015. Points to consider in the development of seed stocks of pluripotent stem cells for clinical applications: International Stem Cell Banking Initiative (ISCBI). Regen Med. 10 (2 Suppl), 1–44.

Andrews, P.W., Ben-David, U., Benvenisty, N., Coffey, P., Eggan, K., Knowles, B.B., et al., 2017. Assessing the safety of human pluripotent stem cells and their derivatives for clinical applications. 9(1). Stem Cell Rep. 11, 1–4.

Augustyniak, J., Zychowicz, M., Podobinska, M., Barta, T., Buzanska, L., 2014. Reprogramming of somatic cells: possible methods to derive safe, clinical-grade human induced pluripotent stem cells. Acta Neurobiol. Exp. (Warsz) 74 (4), 373–382.

Bairoch, A., 2018 Jul. The Cellosaurus, a Cell-Line Knowledge Resource. J. Biomol. Tech. JBT 29 (2), 25–38.

Bard, J., Rhee, S.Y., Ashburner, M., 2005. An ontology for cell types. Genome Biol. 6 (2), R21.
Bar-Nur, O., Russ, H.A., Efrat, S., Benvenisty, N., 2011 Jul 8. Epigenetic memory and preferential lineage-specific differentiation in induced pluripotent stem cells derived from human pancreatic islet beta cells. Cell Stem Cell 9 (1), 17–23.
Bauer, G., Elsallab, M., Abou-El-Enein, M., 2018 Sep Sep. Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions. Stem Cells Transl Med. 7 (9), 676–685.
Ben-David, U., Arad, G., Weissbein, U., Mandefro, B., Maimon, A., Golan-Lev, T., et al., 2014. Aneuploidy induces profound changes in gene expression, proliferation and tumorigenicity of human pluripotent stem cells. Nat. Commun. 8 (5), 4825.
California Institute for Regenerative Medicine (CIRM). For Patients [Internet]. Available from: https://www.cirm.ca.gov/patients.
Carvalho, A.S., Ramalho-Santos, J., 2013. How can ethics relate to science? The case of stem cell research. Eur. J. Hum. Genet. EJHG 21 (6), 591–595.
Charo, R.A., Sipp, D., 2018 Feb 8. Rejuvenating regenerative medicine regulation. N. Engl. J. Med. 378 (6), 504–505.
ClinicalTrials.gov search result on “adult stem cells” [Internet]. [cited 2018 Nov 26]. Available from: https://clinicaltrials.gov/ct2/results/details?term=adult+stem+cells&intr=adult+stem+cell.
CRACK IT, National Centre for the Replacement Refinement & Reduction of Animals in Research. Challenge 6: BADIPS [Internet]. [cited 2019 Feb 20]. Available from: https://crackit.org.uk/challenge-6-badips.
CRACK IT, National Centre for the Replacement Refinement & Reduction of Animals in Research. Challenge 12: UnTangle [Internet]. [cited 2019 Feb 20]. Available from: https://crackit.org.uk/challenge-12-untangle.
Cuende, N., Rasko, J.E.J., Koh, M.B.C., Dominici, M., Ikonomou, L., 2018. Cell, tissue and gene products with marketing authorization in 2018 worldwide. Cytotherapy 20 (11), 1401–1413.
De Sousa, P.A., Steeg, R., Wachter, E., Bruce, K., King, J., Hoeve, M., et al., 2017. Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC) - the Hot Start experience. Stem Cell Res. 20, 105–114.
den Dunnen, J.T., Dalgleish, R., Maglott, D.R., Hart, R.K., Greenblatt, M.S., McGowan-Jordan, J., et al., 2016. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum. Mutat. 37 (6), 564–569.
Du, L., Rachul, C., Guo, Z., Caulfield, T., 2016 Jun Jun. Gordie Howe’s “Miraculous Treatment”: Case Study of Twitter Users’ Reactions to a Sport Celebrity’s Stem Cell Treatment. JMIR Public Health Surveill. 2 (1), e8.
ECMA International. Standard ECMA-404: The JSON Data Interchange Syntax, 2nd edition [Internet]. 2017. Available from: https://www.ecma-international.org/publications/files/ECMA-ST/ECMA-404.pdf.
European Molecular Biology Laboratory - European Bioinformatics Institute. BioSamples [Internet]. Available from: https://www.ebi.ac.uk/biosamples.
EuroStemCell. EuroStemCell [Internet]. Available from: https://www.eurostemcell.org/.
fairsharing.org. Persistent identifier for hPSCreg from fairsharing.org [Internet]. Available from: https://fairsharing.org/biodbcore-001157/.
Fate Therapeutics. A Pluripotent Cell Platform for Enabling an Off-the-Shelf Engineered Immunotherapy Revolution [Internet]. [cited 2019 Mar 10]. Available from: https://fatetherapeutics.com/science/ipsc-product-platform/.
Faulconbridge, A., Burdett, T., Brandizi, M., Gostev, M., Pereira, R., Vasant, D., et al., 2014. Updates to BioSamples database at European Bioinformatics Institute. Nucleic Acids Res. 42 (Database issue):D50-52.
Fielding, Roy Thomas. Architectural Styles and the Design of Network-based Software Architectures [Internet]. University of California, Irvine; 2000. Available from: http://www.ics.uci.edu/~fielding/pubs/dissertation/rest_arch_style.htm.
FORCE11. The FAIR Data Principles [Internet]. [cited 2018 Nov 27]. Available from: https://www.force11.org/group/fairgroup/fairprinciples.
Fujibuchi Laboratory. Integrated Collection of Stem Cell Bank data [Internet]. Available from: http://icscb.stemcellinformatics.org/.
Fujifilm. Cellular Dynamics [Internet]. Available from: https://fujifilmcdi.com.
Glassberg, M.K., Csete, I.S., Toonkel, R.L., 2018 Jun Jun. High Stakes: Direct to Consumer Marketing of Unproven Stem Cell Treatments for Lung Disease. Chest 153 (6), 1294–1295.
Global Alliance for Genomics and Health. Automatable Discovery and Access Matrix (ADA-M) [Internet]. [cited 2018 Nov 27]. Available from: https://www.ga4gh.org/genomic-data-toolkit/regulatory-ethics-toolkit/.
Global Alliance for iPSC Therapies (GAiT). The Global Alliance for induced Pluripotent Stem Cell Therapies [Internet]. Available from: http://www.gait.global.
Globe Newswire. Thyas Obtains Exclusive Rights to Manufacture Induced Pluripotent Stem Cells-Derived Killer T Cells for Autologous Immunotherapy [Internet]. 2019 [cited 2019 Mar 10]. Available from: https://globenewswire.com/news-release/2019/01/17/1701245/0/en/Thyas-Obtains-Exclusive-Rights-to-Manufacture-Induced-Pluripotent-Stem-Cells-Derived-Killer-T-Cells-for-Autologous-Immunotherapy.html.
Gonzalez, R., Garitaonandia, I., Poustovoitov, M., Abramihina, T., McEntire, C., Culp, B., et al., 2016. Neural stem cells derived from human parthenogenetic stem cells engraft and promote recovery in a nonhuman primate model of Parkinson’s disease. Cell Transp. 25 (11), 1945–1966.
Guhr, A., Kobold, S., Seltmann, S., Seiler Wulczyn, A.E.M., Kurtz, A., Löser, P., 2018 Aug 14. Recent Trends in Research with Human Pluripotent Stem Cells: Impact of Research and Use of Cell Lines in Experimental Research and Clinical Trials. Stem Cell Rep. 11 (2), 485–496.
Gunter, K.C., Caplan, A.L., Mason, C., Salzman, R., Janssen, W.E., Nichols, K., et al., 2010 Dec Dec. Cell therapy medical tourism: time for action. Cytotherapy. 12 (8), 965–968.
Harvard Catalyst. eagle-i [Internet]. Available from: https://www.eagle-i.net.
Hayek, Mary. A Study to Evaluate the Safety of Neural Stem Cells in Patients With Parkinson’s Disease [Internet]. [cited 2018 Nov 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT02452723.
identifiers.org. Persistent identifier to hPSCreg from identifiers.org [Internet]. Available from: https://www.ebi.ac.uk/miriam/main/datatypes/MIR:00000674.
International Society for Stem Cell Research (ISSCR). Professional Resources [Internet]. Available from: http://www.isscr.org/professional-resources/.
International Society for Stem Cell Research (ISSCR). A Closer Look at Stem Cells [Internet]. Available from: https://www.closerlookatstemcells.org/.
Internet Engineering Task Force (IETF). The JavaScript Object Notation (JSON) Data Interchange Format [Internet]. 2017. Available from: https://tools.ietf.org/html/rfc8259.
International Stem Cell Forum. International Stem Cell Banking Initiative (ISCBI) [Internet]. Available from: http://www.stem-cell-forum.net/initiatives/international-stem-cell-banking-initiative.
International Stem Cell Forum. International Stem Cell Initiative (ISCI) [Internet]. Available from: http://www.stem-cell-forum.net/initiatives/isci/.
International Society for Cell & Gene Therapy (ISCT). ISCT Presidential Task Force - on the use of unproven and/or unethical cell & gene therapy [Internet]. Available from: http://www.isct-unprovencellulartherapies.org/.
Japan approves world-first trial using iPS cells to treat spinal cord injuries. The Japan Times [Internet]. 2019 Feb 18 [cited 2019 Feb 20]; Available from: https://www.japantimes.co.jp/news/2019/02/18/national/science-health/japan-approves-world-first-trial-using-ips-stem-cells-treat-spinal-cord-injuries/#.XG12VYV7lhE.
Keep off-target effects in focus. Nat Med. 2018 Aug;24(8):1081.
Kim, K., Zhao, R., Doi, A., Ng, K., Unternaehrer, J., Cahan, P., et al., 2011 Nov 27. Donor cell type can influence the epigenome and differentiation potential of human induced pluripotent stem cells. Nat. Biotechnol. 29 (12), 1117–1119.
Knoepfler, P.S., Turner, L.G., 2018 Jan Jan. The FDA and the US direct-to-consumer marketplace for stem cell interventions: a temporal analysis. Regen Med. 13 (1), 19–27.
Köhler S, Vasilevsky NA, Engelstad M, Foster E, McMurry J, Aymé S, et al. The Human Phenotype Ontology in 2017. Nucleic Acids Res. 2017 04;45(D1):D865–76.
Kurtz, Andreas, Elsallab, Magdi, Sanzenbacher, Ralf, Abou-El-Enein, Mohamed, 2019. Linking Scattered Stem Cell-Based Data to Advance Therapeutic Development. Trends Mol. Med. https://doi.org/10.1016/j.molmed.2018.10.008.
Kurtz, A., Seltmann, S., Bairoch, A., Bittner, M.-S., Bruce, K., Capes-Davis, A., et al., 2018 Jan 9. A Standard Nomenclature for Referencing and Authentication of Pluripotent Stem Cells. Stem Cell Rep. 10 (1), 1–6.
Lanza, R., Russell, D.W., Nagy, A., 2019. Engineering universal cells that evade immune detection. Nat. Rev. Immunol. 19, 723–733. https://doi.org/10.1038/s41577-019-0200-1.
Lee, J.-H., Lee, J.B., Shapovalova, Z., Fiebig-Comyn, A., Mitchell, R.R., Laronde, S., et al., 2014 Dec. Somatic transcriptome priming gates lineage-specific differentiation potential of human-induced pluripotent stem cell states. Nat. Commun. 3 (5), 5605.
Malone, J., Holloway, E., Adamusiak, T., Kapushesky, M., Zheng, J., Kolesnikov, N., et al., 2010 Apr 15. Modeling sample variables with an Experimental Factor Ontology. Bioinforma Oxford Engl. 26 (8), 1112–1118.
Mandai, M., Watanabe, A., Kurimoto, Y., Hirami, Y., Morinaga, C., Daimon, T., et al., 2017. Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. 376(11). N. Engl. J. Med. 16, 1038–1046.
Marsh, S.G.E., Albert, E.D., Bodmer, W.F., Bontrop, R.E., Dupont, B., Erlich, H.A., et al., 2010 Apr. Nomenclature for factors of the HLA system, 2010. Tissue Antigens 75 (4), 291–455.
Mehat, M.S., Sundaram, V., Ripamonti, C., Robson, A.G., Smith, A.J., Borooah, S., et al., 2018 Nov Nov. Transplantation of human embryonic stem cell-derived retinal pigment epithelial cells in macular degeneration. Ophthalmology 125 (11), 1765–1775.
Menasché, P., Vanneaux, V., Hagège, A., Bel, A., Cholley, B., Parouchev, A., et al., 2018 Jan 30. Transplantation of Human Embryonic Stem Cell-Derived Cardiovascular Progenitors for Severe Ischemic Left Ventricular Dysfunction. J. Am. Coll. Cardiol. 71 (4), 429–438.
Merkle, F.T., Ghosh, S., Kamitaki, N., Mitchell, J., Avior, Y., Mello, C., et al., 2017. Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations. Nature 545 (7653), 229–233.
Mitjavila-Garcia, M.T., Simonin, C., Peschanski, M., 2005. Embryonic stem cells: meeting the needs for cell therapy. Adv. Drug Deliv. Rev. 57 (13), 1935–1943.
Morrison, M., Klein, C., Clemann, N., Collier, D.A., Hardy, J., Heisserer, B., et al., 2015 Oct Oct. StemBANCC: Governing Access to Material and Data in a Large Stem Cell Research Consortium. Stem Cell Rev. 11 (5), 681–687.
Murdoch, B., Zarzeczny, A., Caulfield, T., 2018. Exploiting science? A systematic analysis of complementary and alternative medicine clinic websites’ marketing of stem cell therapies. BMJ Open 8 (2), e019414.
NCBI. Pubmed Identifier [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pmc/about/public-access-info/.
Petricciani, J., Hayakawa, T., Stacey, G., Trouvin, J.-H., Knezevic, I., 2017 Nov. Scientific considerations for the regulatory evaluation of cell therapy products. Biol. J. Int. Assoc. Biol. Stand. 50, 20–26.
Public Health England. The European Collection of Authenticated Cell Cultures (ECACC) [Internet]. [cited 2019 Jan 7]. Available from: https://www.phe-culturecollections.org.uk/collections/ecacc.aspx.
Rachul, C., Caulfield, T., 2015 Oct Oct. Gordie Howe’s Stem Cell “Miracle”: A Qualitative Analysis of News Coverage and Readers’ Comments in Newspapers and Sports Websites. Stem Cell Rev. 11 (5), 667–675.
re3data.org. Persistent identifier for hPSCreg in re3data [Internet]. Available from: http://doi.org/10.17616/R36B9H.
Reardon, S., Cyranoski, D., 2014 Sep 18. Japan stem-cell trial stirs envy. Nature 513 (7518), 287–288.

Reisman, M., Adams, K.T., 2014 Dec. Stem cell therapy: a look at current research, regulations, and remaining hurdles. P T Peer-Rev. J. Formul. Manage. 39 (12), 846–857.
RIKEN. RIKEN [Internet]. Available from: http://www.riken.jp/en/.
Rubin, R., 2018 Oct 9. Unproven but Profitable: The Boom in US Stem Cell Clinics. JAMA 320 (14), 1421–1423.
RUCDR Infinite Biologics. RUCDR Infinite Biologics [Internet]. Available from: https://www.rucdr.org/.
Sakurai, K., Kurtz, A., Stacey, G., Sheldon, M., Fujibuchi, W., 2016. First proposal of minimum information about a cellular assay for regenerative medicine. Stem Cells Transl. Med. 5 (10), 1345–1361.
Schwartz, S.D., Regillo, C.D., Lam, B.L., Eliott, D., Rosenfeld, P.J., Gregori, N.Z., et al., 2015 Feb 7. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet Lond Engl. 385 (9967), 509–516.
Seltmann, S., Lekschas, F., Müller, R., Stachelscheid, H., Bittner, M.-S., Zhang, W., et al., 2016 Jan 4. hPSCreg-the human pluripotent stem cell registry. Nucleic Acids Res. 44 (D1), D757–D763.
Sipp, D., Caulfield, T., Kaye, J., Barfoot, J., Blackburn, C., Chan, S., et al., 2017. Marketing of unproven stem cell-based interventions: A call to action. Sci. Transl. Med. 5 (9), 397.
Song, W.K., Park, K.-M., Kim, H.-J., Lee, J.H., Choi, J., Chong, S.Y., et al., 2015 May 12. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients. Stem Cell Rep. 4 (5), 860–872.
Stemcell Knowledge & Information Portal (SKIP). Stemcell Knowledge & Information Portal [Internet]. Available from: https://skip.stemcellinformatics.org/en/.
Streeter, I., Harrison, P.W., Faulconbridge, A., The HipSci Consortium, Flicek, P., Parkinson, H., et al., 2017. The human-induced pluripotent stem cell initiative-data resources for cellular genetics. Nucleic Acids Res. 04;45(D1):D691–7.
Sugarman, J., Barker, R.A., Kerridge, I., Lysaght, T., Pellegrini, G., Sipp, D., et al., 2018 Nov 13. Tackling ethical challenges of premature delivery of stem cell-based therapies: ISSCR 2018 annual meeting focus session report. Stem Cell Rep. 11 (5), 1021–1025.
Sullivan, S., Stacey, G.N., Akazawa, C., Aoyama, N., Baptista, R., Bedford, P., et al., 2018 Oct Oct. Quality control guidelines for clinical-grade human induced pluripotent stem cell lines. Regen Med. 13 (7), 859–866.
Sullivan, S., in press. Pluripotent stem cell banking for research and specialist applications. Stem Cell Res.
Takahashi, K., Yamanaka, S., 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126 (4), 663–676.
The Asahi Shimbun. Osaka team gets nod for world's 1st iPS cell-based heart treatment [Internet]. 2018 [cited 2019 Mar 10]. Available from: http://www.asahi.com/ajw/articles/AJ201805170029.html.
The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [Internet]. [cited 2018 Oct 31]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf.
The European Parliament and the Council of the European Union. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [Internet]. [cited 2019 Jan 2]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0023&from=EN.
The Human Pluripotent Stem Cell Registry (hPSCreg). Cell Line Registration Quick-Start Guide [Internet]. [cited 2018 Nov 27]. Available from: https://hpscreg.eu/docs/downloads/QuickStartGuideCellLineRegistration.pdf.
The Human Pluripotent Stem Cell Registry (hPSCreg). hPSCreg Documents and Governance [Internet]. 2019. Available from: https://hpscreg.eu/about/documents-and-governance.
Thomas, E.D., 1999. A history of haemopoietic cell transplantation. Br. J. Haematol. 105 (2), 330–339.
ViaCyte. Center for Beta Cell Therapy in Diabetes and ViaCyte Announce Start of European Clinical Trial of Human Stem Cell-derived Implants in Type 1 Diabetes Patients. 2019.
Wang, Y.-K., Zhu, W.-W., Wu, M.-H., Wu, Y.-H., Liu, Z.-X., Liang, L.-M., et al., 2018 Jul 10. Human Clinical-Grade Parthenogenetic ESC-Derived Dopaminergic Neurons Recover Locomotive Defects of Nonhuman Primate Models of Parkinson's Disease. Stem Cell Rep. 11 (1), 171–182.
Wetterstrand, KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) [Internet]. [cited 2018 Nov 13]. Available from: https://www.genome.gov/sequencingcostsdata/.
Wilkinson, M.D., Dumontier, M., Aalbersberg, I.J.J., Appleton, G., Axton, M., Baak, A., et al., 2016 Mar Mar. The FAIR Guiding Principles for scientific data management and stewardship. Sci. Data 15 (3), 160018.
Wilmut, I., Leslie, S., Martin, N.G., Peschanski, M., Rao, M., Trounson, A., et al., 2015. Development of a global network of induced pluripotent stem cell haplobanks. Regen Med. 10 (3), 235–238.
Wu, Y.-L., Pandian, G.N., Ding, Y.-P., Zhang, W., Tanaka, Y., Sugiyama, H., 2013. Clinical grade iPS cells: need for versatile small molecules and optimal cell sources. Chem. Biol. 20 (11), 1311–1322.
Zheng, Y.L., 2016. Some ethical concerns about human induced pluripotent stem cells. Sci. Eng. Ethics 22 (5), 1277–1284.